Critical care management of patients with end-stage liver disease

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Objectives: **To review the management of complications related to end-stage liver disease in the intensive care unit. The goal of this review is to address topics important to the practicing physician.**

Data Sources: **We performed an organ system-based PubMed literature review focusing on the diagnosis and treatment of critical complications of end-stage liver disease.**

Data Synthesis and Findings: **When available, preferential consideration was given to randomized controlled trials. In the absence of trials, observational and retrospective studies and consensus opinions were included. We present our recommendations for the neurologic, cardiovascular, pulmonary, gastrointestinal, renal, and infectious complications of end-stage liver disease.**

Conclusions: **Complications related to end-stage liver disease have significant morbidity and mortality. Management of these complications in the intensive care unit requires awareness and expertise among physicians from a wide variety of fields. (Crit Care Med 2011; 39:1157–1166)**

Key Words: end-stage liver disease; encephalopathy; hepatorenal syndrome; variceal bleeding; hepatopulmonary syndrome; portopulmonary hypertension; decompensated cirrhosis; portosystemic encephalopathy

The onset of complications related to end-stage liver disease (ESLD) defines the transition from a compensated to decompensated state. Critically ill patients with ESLD admitted to the intensive care unit (ICU) have an overall mortality rate ranging from 50% to 100% (1–5). Patients with ESLD usually are referred for transplantation evaluation when their model for ESLD scores are ten or they have a major complication develop that is related to liver disease, such as hepatic encephalopathy, ascites, or variceal bleeding (6). Patients with ESLD admitted to the ICU who are not candidates for liver transplantation have a particularly poor long-term prognosis, even if they survive the ICU admission. In this concise review, we review key organ systems and discuss specific ESLD complications and management. Discussion of specific causes of liver disease such as viral hepatitis, alcoholic hepatitis, acute on chronic liver disease, and fulminant hepatic failure are beyond the scope of this review.

COMPLICATIONS

Neurologic

Hepatic encephalopathy (HE) is defined as a neuropsychiatric disorder of altered consciousness in patients with liver disease, and it occurs as a result of portosystemic shunting and hepatocellular dysfunction. Patients with HE are at increased aspiration risk, which leads to acute respiratory failure. Management of HE primarily involves identification and prompt correction of precipitating factors, such as infection, gastrointestinal bleeding, and electrolyte and acid–base disturbances, because most acute HE episodes are attributable to precipitating factors rather than natural progression of ESLD. Lactulose administered orally or rectally is frequently used as first-line treatment for HE (7). Lactulose increases bowel movement frequency, which decreases ammonia precursors in the gastrointestinal tract (8). In addition, lactulose acidifies bowel content, which slows ammonia absorption and reduces blood ammonia levels. Lactulose also modifies bowel flora, favoring *Lactobacillus* over urease and protease-splitting bacteria (9). Although some studies have shown lactulose to be effective in improving and decreasing recurrence of HE, meta-analyses of randomized controlled trials have challenged lactulose's efficacy (10), and none has demonstrated a positive effect on survival (10–12). Despite lack of clear efficacy data, neomycin and metronidazole are frequently administered as second-line therapy for HE. Studies have demonstrated that rifaximin significantly improved blood ammonia level (13), concentrations of benzodiazepine-like compounds (14), and mental status (13) when compared with lactulose. However, a recent meta-analysis showed no difference between rifaximin and lactulose in improving HE (15). In the outpatient setting, treatment with rifaximin and lactulose maintained remission from HE and significantly reduced hospitalization attributable to HE when compared to lactulose and placebo (16). However, the results of this study are not clearly generalizable to ICU patients. Whenever possible, oral/enteral nutrition without protein restriction should be considered (17). Probiotics (18, 19), acarbose (20), ornithine-aspartate (21–23), and sodium benzoate (24) may be considered in treating HE. In our ICU, after focusing on precipitating factors and implementing aspiration precautions, we treat episodes of acute HE with oral or rectal lactulose to achieve four to five loose bowel movements per day, with adjunctive use of neomycin, metronidazole, or rifaximin if lactulose is refractory. Finally, small studies have shown that treatment with the molecular adsorbent recalculating system improves HE. However, larger studies that include cost-effectiveness are needed before we can recommend its use (25–27).

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Cardiovascular

Although the general approach in critically ill ESLD patients to hypotension and other cardiovascular crises is the same as with any critically ill patient (28, 29), several unique aspects of ESLD merit attention. First, ESLD patients typically have a hyperdynamic vasodilated cardiovasculature, which usually manifests clinically as low baseline blood pressure and high cardiac output (30, 31). Although the exact mechanisms are still being investigated, this characteristic hyperdynamic state is generally attributed to splanchnic and peripheral vasodilation and arteriovenous communications, with subsequent reduction in effective circulating blood volume, activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, and, consequently, renal artery vasoconstriction, and sodium and fluid retention (32, 33). As liver disease worsens, so, too, does the cardiovascular pathophysiology. Second, it has long-been recognized that ESLD patients can quickly decompensate, even after relatively minor physiologic stress. Recently, this pathophysiology has been termed "cirrhotic cardiomyopathy" (34, 35). Although no official consensus definition exists, cirrhotic cardiomyopathy has been described as cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress or altered diastolic relaxation or both with electrophysiological abnormalities (mainly prolongation of the QT interval) in the absence of other known cardiac disease (such as alcoholic cardiomyopathy) (33). Although most cases are subclinical, this condition can manifest as unexpected physiologic deterioration such as heart failure, renal failure, and cardiovascular collapse in response to physiologic stress, such as surgery, infection (36, 37), and transjugular intrahepatic portosystemic shunt (TIPS) (38). Paracentesis-induced circulatory dysfunction, although thought to be mainly caused by increased postparacentesis splanchnic arteriolar vasodilation (39), may be partly attributable to occult cardiomyopathy. Once overt heart failure manifests, treatment is supportive and should follow the general principles of heart failure management. It is also important to recognize that approximately 30% of liver transplant candidates have significant coronary artery disease and that exclusion of such is essential before diagnosing cirrhotic cardiomyopathy. Conceptually, this is similar to excluding all other causes of renal failure before diagnosing hepatorenal syndrome. Third, autonomic dysfunction is common in cirrhotic patients and, in addition to impaired sympathetic response (40), can manifest as impaired myocardial contractility in response to orthostasis (41) and reduced response to vasoconstrictors (42, 43). Careful titration of inotropes and vasopressors therefore is especially necessary in ESLD patients. In addition, use of β-blockers in patients with known varices can blunt tachycardia. Fourth, although controversial, some evidence suggests ESLD patients are more prone to relative adrenal insufficiency (44, 45). We concur with the 2008 Surviving Sepsis Campaign Guidelines recommendation to not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it, and its suggestion that intravenous corticosteroids for adult septic shock be considered when hypotension responds poorly to adequate fluid resuscitation and vasopressors (46). Fifth, we generally concur with existing guidelines for critically ill patients (28, 29, 46) that prioritize early recognition and treatment of shock, broadly equate isotonic crystalloid and colloid solutions, and recommend targeting specific resuscitation end points such as central venous oxygen saturation and mean arterial pressure. Based on ESLD physiology (low serum albumin, total fluid overload with relative intravascular hypovolemia) and tradition, albumin is commonly used; however, outcomes evidence for resuscitation superiority in ESLD patients is limited. Last, we emphasize that although ESLD patients tend to clear lactate more slowly, compensated ESLD patients have normal or near-normal lactate levels at rest; therefore, elevated lactate in an ESLD patient should be considered as seriously as it is in any other patient (47).

The astute clinician therefore should determine an ESLD patient's usual blood pressure, investigate cardiac output in an apparently low-normal to normal range, watch for heart failure and decompensation in response to even minor stress, anticipate atypical hemodynamic response to vasoactive agents, consider corticosteroids for refractory shock, and recognize that an elevated lactate in an ESLD patient merits investigation.

Pulmonary

Hepatopulmonary syndrome is defined by the presence of hypoxia attributable to ventilation–perfusion mismatch, intrapulmonary shunting, pulmonary capillary vasodilation, and limitation of oxygen diffusion in patients with ESLD and portal hypertension (48–52). Based on animal models, nitric oxide may play an important role in the development of pulmonary vascular dilation (53). Other proposed factors include endothelin-1–induced nitric oxide overproduction, intestinal endotoxemia with tumor necrosis factor overproduction, hemeoxygenase-1, and endothelial-derived hyperpolarizing factor (54). Current therapy for hepatopulmonary syndrome is limited to supplemental oxygen. TIPS may result in improvement in hepatopulmonary syndrome, but this has been inconsistent (55). Liver transplantation remains the definitive treatment that improves symptoms and survival (54, 56, 57).

Portopulmonary hypertension (PPHTN) is defined as pulmonary arterial hypertension attributable to increased pulmonary vascular resistance in the presence of portal hypertension and a pulmonary capillary wedge pressure <15 mm Hg (58–60). The prevalence of PPHTN ranges from 3.5% to 16% and is usually diagnosed during liver transplantation evaluation (61–66). Vasoactive substances that are metabolized in the liver travel to the pulmonary circulation via portosystemic shunts, causing vasoconstriction (67, 68). Patients with moderate (mean pulmonary artery pressure, 35–45 mm Hg) to severe (mean pulmonary artery pressure >45 mm Hg) PPHTN are at high risk for graft failure after transplantation because of venous congestion and right ventricular dysfunction (69, 70). Vasodilators, vascular growth, and remodeling agents are considered for treatment (71, 72), including epoprostenol (73–79), bosentan (80–85), sildenafil (86, 87) and iloprost (83, 88, 89). In our institution, we use epoprostenol infusion titrated to maintain mean pulmonary artery pressure <25 mm Hg guided by pulmonary artery catheter. Once we achieve goal mean pulmonary artery pressure, patients are maintained on the corresponding dose until transplantation. The majority of patients with PPHTN who have successfully undergone liver transplantation have demonstrated improvement or complete normalization of their pulmonary artery pressures (69, 75, 79, 90, 91).

Table 1. Portopulmonary hypertension versus hepatopulmonary syndrome

	Portopulmonary Hypertension	Hepatopulmonary Syndrome
Presence of portal hypertension	Yes	Yes
Cause	Pulmonary vascular vasoconstriction	Right to left shunt
	Endothelial smooth muscle proliferation	Pulmonary vascular dilation
	In situ thrombosis and fibrosis	
	Remodeling of arterial wall	
Presence of right heart failure	Happens at late stage	None present
Presence of pulmonary hypertension	Yes	No
Diagnosis	Excertional dyspnea	Platypnea
	Fatigue	Orthodeoxia
	Syncope and chest pain in severe cases	Normal pulmonary hemodynamics
	High mean pulmonary artery pressure	Right-to-left shunt on echocardiography
	High pulmonary vascular resistance	Decrease carbon monoxide diffusion capacity
		Intrapulmonary vascular dilation on pulmonary angiogram
Treatment	Vasodilators	Oxygen
	Liver transplantation	Liver transplantation
		Embolization of shunt in selected cases
Resolution after liver transplantation	Yes but may take months to years	Yes

However, patients with severe PPHTN are likely to have fixed pathologic changes in the pulmonary vasculature that may not be reversible with liver transplantation and is associated with a high perioperative mortality rate (65, 92). Last, TIPS can potentially worsen PPHTN, and a careful weighing of risks and benefits is essential. Table 1 addresses the difference between PPHTN and hepatopulmonary syndrome.

Patients with ESLD who have acute respiratory distress syndrome (ARDS) develop have significantly higher mortality when compared with patients with ARDS without ESLD (93). Primary ARDS can occur after aspiration of blood or gastric content, most often in patients with significant HE. Secondary ARDS is caused by a nonpulmonary insult that results in increased inflammatory cytokines and pulmonary dysfunction. Secondary ARDS can be caused by infection, shock, ischemia reperfusion injury during liver transplantation, and massive blood transfusion. Circulating cytokines such as tumor necrosis factor, interleukin-1, and interleukin-6 are increased in patients with ESLD and place cirrhotic patients at increased risk for ARDS (94). Management of patients with ARDS is mainly supportive. Several interventions such as inhaled nitric oxide, prone ventilation, and high-frequency oscillatory ventilation have been shown to improve oxygenation but not survival, and they can be considered as rescue therapy (95). Avoidance of barotrauma, volutrauma, and ventilator dyssynchrony is important. Recruitment maneuvers and high positive end-expiratory pressure should be used with caution in patients with a pneumothorax or patients in shock (95). The only intervention shown to improve mortality is a lung-protective strategy using low tidal volume (96).

Mechanical factors contribute to respiratory failure in ESLD. Patients can present with several symptoms related to hydrothorax or tense ascites, such as dyspnea and abdominal discomfort. To manage tense ascites, large-volume paracentesis should be performed with concurrent administration of albumin (6–8 g albumin for every liter of fluid removed) (96–99). Hepatic hydrothorax can result from the passage of ascites from the peritoneal to the pleural cavity through small defects in the tendinous portion of the diaphragm (100). Spontaneous bacterial empyema is defined as culture-positive pleural fluid or the presence of a polymorphonuclear count >500 cells/μL in the setting of cirrhosis and the absence of parapneumonic effusion. Incentive spirometry and positive pressure breathing including mechanical ventilation help resolving atelectasis and lung collapse. For patients with hepatic hydrothorax, initial management consists of sodium restriction and diuretics. Respiratory compromise or suspicion of spontaneous bacterial empyema merit thoracentesis. We typically place small "pig tail" catheters using ultrasound guidance. Compared with serial thoracenteses, this approach allows continuous drainage without repeat punctures. To minimize risk of infection, we remove the pig tail catheter once drainage is minimal or after a few days have passed. In refractory cases of ascites or hydrothorax, we recommend TIPS (101–106). Diaphragmatic repair involving a pleural flap and surgical mesh reinforcement also have been used as a treatment option (107). Liver transplantation is the definitive treatment. However, peritoneovenous shunt may be considered for patients with refractory ascites/hydrothorax who are not candidates for repeat paracenteses, transplantation, or TIPS (108, 109). Last, although existing data conflict, some evidence suggests that hyperbilirubinemia distorts pulsoximetry readings (110–112). We therefore recommend obtaining somewhat more frequent arterial blood gas levels in the presence of hyperbilirubinemia when clinically indicated.

Gastrointestinal Bleeding

Gastrointestinal bleeding can be a devastating complication of ESLD and portal hypertension. There are several causes of upper and lower gastrointestinal bleeding in ESLD; however, we limit our discussion to esophageal and gastric varices. Gastrointestinal bleeding attributable to varices has high morbidity and mortality rates (113–115). Patients should be admitted to the ICU and several steps should be taken, such as obtaining adequate venous access (peripheral or central or both), volume resuscitation, blood transfusion, vasoconstrictors, prophylactic antibiotics, and urgent therapeutic endoscopy. Although not clearly supported by the literature, many endoscopists, including those at our institution, request administration of blood products/vitamin K to correct coagulopathy before endoscopy. In our ICU, we typically intubate all ESLD patients with active upper

gastrointestinal bleeding before endoscopy to minimize aspiration risk and facilitate endoscopy. This approach also avoids the dangerous scenario of massive hematemesis during endoscopy, requiring an emergent and often difficult intubation. Medical management of variceal bleeding aims at rapidly decreasing portal pressure and consists of splanchnic vasoconstrictors such as terlipressin (not available in the United States), vasopressin, and octreotide (116–119). Although physiologically rational, venodilators (nitrates and β-blockers) are rarely used because of their potent effect on systemic blood pressure in an already unstable bleeding patient (120). Right upper quadrant ultrasound with Doppler is a useful noninvasive test to evaluate hepatic and portal vascular patency for TIPS consideration. Antibiotic prophylaxis for 7 days has been shown to decrease spontaneous bacterial peritonitis, sepsis, recurrent bleeding, hospital length of stay, and all-cause mortality (121–125). Antibiotic choice should be made considering local bacterial resistance profile and treatment cost. Balloon tamponade is an effective temporizing measure in stopping variceal bleeding and should be considered if endoscopic intervention is ineffective or if the patient is too unstable to undergo endoscopy. Misplacement of the tube, perforation, and necrosis are known complications. Endoscopic esophageal variceal band ligation (EBL) is life-saving, is preferred over sclerotherapy, and should be performed as soon as the patient is resuscitated, preferably within 12 hrs (126–128). It is well-established that the combination of EBL and medical therapy is more effective than EBL alone (129). If the gastrointestinal bleeding is from gastric varices, then endoscopic treatment with tissue adhesives has been shown effective in controlling bleeding and should be considered (130, 131). However, TIPS should be considered as first-line treatment if adhesive agents are unavailable or if the operator is not experienced in that procedure (132). Measuring hepatic venous pressure gradient within 24 hrs of variceal bleeding is helpful in predicting treatment failure and the need for rescue therapy (115). TIPS is effective in the immediate control of variceal bleeding, with a success rate of almost 95% and with recurrent bleeding in only 12% (133). Encephalopathy and heart failure can develop after TIPS because of shunting of blood from the portal to the systemic circulation. TIPS has traditionally been recommended as a rescue therapy for failed endoscopic management. However, TIPS within 72 hrs of variceal bleeding in addition to EBL has been shown in a recent study to be effective in preventing recurrent bleeding and has improved short-term and long-term survival in ESLD patients with Childs C status, or Childs B with active bleeding during endoscopy (134). Of importance, there was no increase in encephalopathy, heart failure, or any other complications in the TIPS-treated patients compared to EBL alone (134). TIPS should aim to decrease hepatic venous pressure gradient to $<$12 mm Hg if possible, and extended polytetrafluoroethylene stents, which have a better patency profile compared to bare metal stent, should be used (135, 136). Surgical shunts are reserved for patients in whom EBL fail and in whom TIPS is not possible because of thrombosis of portal vein or hepatic vein or both (137).

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is defined as acute kidney injury in patients with ESLD and ascites in the absence of an identifiable cause of renal failure (138, 139). The diagnosis is made after ruling out infection, hypovolemia, shock, or drug-induced renal failure. In type 1 HRS, there is a rapid deterioration in kidney function, with the serum creatinine increasing by $>$100% from baseline to $>$2.5 mg/dL within a 2-wk period. Type 2 HRS occurs in patients with a steady but moderate degree of renal dysfunction or a deterioration in kidney function that does not fulfill the criteria for HRS type 1 (140). Without liver transplantation, patients who have HRS develop have a median survival time of approximately 3 months; the longer patients have had HRS before transplantation, the less likely they are to recover normal renal function after transplantation (140). High model for ESLD score (141), type 1 HRS (142), and systemic inflammatory response syndrome (143) are the major prognostic factors of mortality in patients with HRS.

Several interventions can prevent and treat HRS, including avoidance of nephrotoxins, adequate volume resuscitation, paracentesis, and vasoconstrictors. Patients with HRS should be optimally volume resuscitated; however, choice of intravenous fluids remains controversial. Intravenous administration of albumin (initially 1 g albumin per kg of body weight, up to a maximum of 100 g, followed by 20–40 g/day) for a maximum of 15 days in combination with terlipressin has been shown to reverse HRS type 1 (144). In patients with spontaneous bacterial peritonitis (SBP), albumin has been reported to improve systemic hemodynamics and to reduce risk of HRS and death (145, 146). The question arises as to whether the beneficial effect observed with albumin is primarily attributable to volume expansion, or whether albumin has additional effects compared to other colloids. In one randomized, unblinded pilot study, albumin was compared to hetastarch in patients with SBP (145). Treatment with albumin was associated with a significant increase in arterial pressure and suppression of plasma renin activity, whereas no significant changes were observed in the hetastarch group (145).

Uncontrolled studies demonstrated an improvement in renal function in patients with HRS after paracentesis (147–149), likely attributable to increased venous return and cardiac function, and reduced renal venous pressure and intrarenal pressure.

Vasoconstriction of the splanchnic vascular beds is believed to reverse HRS by increasing the effective arterial blood volume, thereby suppressing activation of the renin-angiotensin-aldosterone and the sympathetic nervous systems, therefore reversing compensatory renal vasoconstriction and ultimately increasing renal perfusion. Midodrine is an oral α-agonist that is widely used in combination with octreotide and albumin to treat HRS, despite a relative paucity of large trial data (150–155). Although not approved for use in the United States, terlipressin, a vasopressin analog, has been shown effective in reversing HRS. An initial pilot study demonstrated that terlipressin improved glomerular filtration rate in patients with HRS compared to placebo (156). A retrospective European study has demonstrated survival benefit, particularly as a bridge to liver transplantation (157). Other studies confirmed renal function improvement after terlipressin treatment (158, 159). Albumin infusion addition to terlipressin therapy led to a complete response in patients with HRS (160) These preliminary studies led to three randomized prospective trials that established that terlipressin (in combination with albumin) improved renal function in patients with type 1 HRS

(144, 161, 162). However, no overall survival benefit was demonstrated in the two largest studies. Other agents such as vasopressin (163, 164), norepinephrine (75, 165, 166), and N-acetylcysteine (167) may play a role in the management of HRS. Dopamine, prostanoids, natriuretic peptides, and endothelin antagonists have been shown ineffective (168–172). In our institution, medical treatment of HRS consists of oral midodrine and subcutaneous octreotide in addition to albumin. We also use renal replacement therapy as a bridge to liver transplantation in patients in whom medical therapy fails. In HRS patients with tenuous hemodynamics, we prefer continuous veno-venous hemodialysis over intermittent hemodialysis. Treatment with the molecular adsorbent recalculating system has shown to improve renal function in patients with HRS (26, 27).

Infection

Through a variety of mechanisms, including Kupffer cell and neutrophil dysfunction, endotoxemia attributable to gut permeability, and decreased complement levels (173–175), ESLD patients have significant immune dysfunction, higher rates of infection and sepsis, and worse outcomes than general patients (176, 177). A recent review of 178 studies of 11,987 ESLD patients showed that infection quadrupled mortality, with one-third dead by 1 month and another one-third dead by 1 yr (178). Importantly, infection also likely worsens liver function *per se*, including contributing to risk of variceal bleeding (175). We therefore find it clinically useful to consider ESLD patients as functionally immunosuppressed as liver transplantation patients using immunosuppressant medication. We emphasize attention to standard ICU infection prevention measures, have a low threshold for investigating potential infection, and consider risk of multidrug resistance and atypical organisms when choosing antibiotics. Because infection is so often the reason ESLD patients become critically ill, we recommend that in such patients, whenever a procedure is performed in which body fluid can be obtained (e.g., intubation, paracentesis, thoracentesis, central line), cultures should be sent unless the physician has an extremely low concern for infection. Last, as with all critically ill patients, empirical fungal coverage is a challenging clinical decision but should be considered when risk factors, such as persistent fever despite appropriate antibacterial therapy, *Candida* colonization, abdominal surgery, and receipt of dialysis, are present (179, 180).

SBP is the most common infection in ESLD patients and can precipitate decompensation (181). Unfortunately, SBP can present with no or vague symptoms, and physician impression alone cannot exclude SBP (182). Therefore, we recommend that paracentesis should be routinely performed in critically ill ESLD patients with ascites. Concomitant blood cultures should also be drawn because bacteremia is present in approximately half of SBP cases and can help identify the organism (183). Although there is no

Table 2. Complications of end-stage liver disease and management recommendations

Organ System	Complication	Recommendations	References
Neurologic	Hepatic encephalopathy	Identify precipitant(s)	
		Aspiration precautions	
		Lactulose	7–9
		Oral antibiotics	13, 14
Cardiovascular	Cirrhotic cardiomyopathy	Anticipate decompensation	
	Adrenal insufficiency	Consider steroids for fluid-refractory hypotension	44–46
Pulmonary	Hepatopulmonary syndrome	Supportive care	55
	Portopulmonary hypertension	Consider TIPS	
	Acute respiratory distress syndrome	Intravenous epoprostenol	73–79
		Lung-protective ventilation	96
	Mechanical factors (tense ascites, hydrothorax)	Drainage	
		Consider TIPS, surgical shunt if refractory	101–106, 108, 109
Gastrointestinal	Variceal bleeding	Ensure adequate venous access, volume/blood resuscitation	
		Consider intubation and coagulopathy correction	
		Intravenous octreotide for 5 days	116–119
		Antibiotics for 7 days	
		Endoscopic band ligation	121–125
		Liver ultrasound with Doppler	126–128
		If endoscopic band ligation is ineffective or is patient unstable, then balloon tamponade	115
		TIPS	115
		Surgical shunt	115, 134 137
Renal	Hepatorenal syndrome	Exclude other causes of renal failure	
		Ensure adequate volume status	
		Avoid nephrotoxins	
		Paracentesis for tense ascites	
		Octreotide, midodrine, albumin	
		Or	147–149
		Terlipressin, albumin	150–155
		Renal replacement therapy	144, 156–162
Infectious	Sepsis	Treat as immunocompromised	
		Diagnostic paracentesis, antibiotics	
		Consider albumin	146
	Spontaneous bacterial peritonitis		146

TIPS, transjugular intrahepatic portosystemic shunt.

perfect cut-off level, most clinicians use an ascitic fluid polymorphonuclear count of >250 cells/uL as the standard diagnostic cut-off for SBP; white blood cell count >1000 cells/uL, pH <7.35, or blood-ascitic fluid pH gradient ≥0.1 are alternative cut-offs with high positive likelihood ratios (184). Culture-negative neutrocytic ascites (polymorphonuclear >250 cells/uL but culture-negative) and bacterascites (polymorphonuclear <250 cells/uL but culture-positive) should be treated the same as SBP (185). Antibiotic coverage should be directed at Gram-negative aerobic bacteria (*Escherichia coli*, *Klebsiella pneumoniae*) and Gram-positive cocci (Streptococcus, Enterococci). Third-generation cephalosporins are most commonly recommended (185–187), but unit antibiograms and individual patient antibiotic exposure history also should be considered. Although controversial, albumin reduced mortality in one trial (146), whereas a recent observational study suggested albumin may only benefit SBP patients with elevated creatinine, blood urea nitrogen, or total bilirubin (188). Restricting albumin to SBP patients with such evidence of acute kidney injury or worsening liver function is a reasonable approach. It is well-accepted that patients presenting with acute gastrointestinal bleeding should receive empirical antibiotics because such patients are at high risk for SBP, and occult SBP can precipitate gastrointestinal bleeding (185–187). Secondary bacterial peritonitis should be considered if ascitic fluid shows a polymorphonuclear count in the thousands, multiple organisms, or elevated protein levels (185, 186). Lack of clinical improvement despite empirical antibiotics should prompt consideration of abdominal imaging and a repeat paracentesis to look for resistant organisms or secondary bacterial peritonitis or both.

Transplant Candidacy

An ESLD patient's transplant candidacy has overall care implications and realistic goals of care must be communicated to the patient and family. For patients who are not transplant candidates, the goal is restoration of pre-ICU functional status, recognizing that ESLD is an incurable condition without transplantation. For patients listed for transplant, the goal is to provide a "window" of clinical stability when a transplantation could be feasible. For patients who are possible transplant candidates, the goal is to similarly provide a window of opportunity for a candidacy work-up to be completed. We have found the key challenge is keeping this window open, because recurrence of acute illness after resolution of the initial episode is common. Striving to achieve these windows of opportunity must be counterbalanced against potentially futile care and provision of false hope. Frequent and open family communication is essential. We have found it useful to inform families that for a critically ill ESLD patient to achieve a good outcome, the following series of events must take place: 1) resolution of current acute illness; 2) nonrecurrence of another acute illness; 3) for possible candidates, completion of candidacy work-up; 4) availability of suitable organ; 5) successful transplant operation; 6) successful postoperative course; and 7) posthospital discharge with quality of life acceptable to patient. We summarize our recommendations in Table 2.

CONCLUSIONS

There are many organ-specific complications related to ESLD. Emergence of these complications signifies worsening of liver disease and has significant morbidity and mortality. Management of these complications in the ICU requires awareness and expertise among physicians from a wide variety of fields.

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